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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/766,978	Applicant(s) MORTEN, JOHN EDWARD NORRIS	
	Examiner Juliet C. Switzer	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-34 is/are pending in the application.
- 4a) Of the above claim(s) 26-33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14-24 and 34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☒ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 09/977,221.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>5/04 and 8/05</u> | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the paper received on 10/26/06 is acknowledged. In response to a further election requirement to select a single group of polymorphisms for examination, applicant selected a group containing a single polymorphism, that is the polymorphism disclosed at position 1513 of SEQ ID NO: 2.
2. Applicant canceled all pending claims and filed a new set of claims. Newly filed claim 25 falls within the elected group I. New claims 26-30 are within group IV of the original restriction requirement. New claim 31 is within original group III of the original restriction requirement. Claims 14-24 and 32-34 are linking claims which link groups I, III, and IV, as discussed in the original restriction requirement. Claim 32 requires testing to determine the identity of the nucleotide present at a combination of at least two different polymorphic positions, and this is not the elected combination. Claim 33 requires testing to determine the identity of the nucleotide present at each of thirty positions, and this is not the single combination elected. If a claim requiring only the polymorphism at position 1513 of SEQ ID NO: 2 is found to be allowable, rejoinder of these claims will be considered, as appropriate. Thus, claims 14-25, and 34 are examined in this office action.
3. The traversal is on the ground(s) that each of the claimed nucleotide polymorphisms is in the same gene and thus it would not require undue burden to search the art for each individual polymorphism. This is not found persuasive because the individual search and examination of 43 different polymorphisms, even within the same gene poses a substantial burden on the examiner. Polymorphisms are not reported in the literature in any art recognized standard

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format, and the determination of whether or not a given reference teaches a give polymorphism requires separate analysis of each reference. Further, methods for detecting each polymorphism must be given separate consideration under each of the statues. Finally, applicant asserts that because all of the SNP's are within the same gene they should be examined together because they all encode a human P2X7 protein. This is not persuasive because even though all of the single nucleotide polymorphisms are within the same gene, they each would assert their own effect on the activity of the P2X7 nucleic acid sequence which they are contained within, they each have distinct potential prognostic and/or diagnostic effects, and many of them lead to changes in the coding sequence which will lead to the production of proteins whose functionality is unknown. The requirement is still deemed proper and is therefore made FINAL.

Priority

4. Applicant's claim for domestic priority under 35 U.S.C. 120 and 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 14-25, 32, and 34 of this application. The instant specification provides support under 35 U.S.C. 112 for these claims insofar as the specification teaches that the polymorphism at nucleotide 1513 of SEQ ID NO: 2 causes loss of function in P2X₇ (p. 21, lines 4-5), a receptor which is a ligand-gated cation-selective channel that mediates ATP-induced apoptosis of cells. However, the provisional application does not provide adequate support for the claimed invention under 112 1st paragraph, nor do either of the foreign priority documents (see rejections herein under 112 1st paragraph). Therefore, the filing date of the instant application is considered to be the instant filing date of the parent application 09/977221, 10/16/2001. It is of interest to note that the fact that the polymorphism at position 1513 of SEQ

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ID NO: 2 causes loss of function of P2X₇ is first disclosed in foreign priority document filed 4/6/01.

Specification

6. The disclosure is objected to because of the following informalities: The information in the table on pages 17-19 is misaligned. The spacing between the lines in the "polymorphism" column is not the same as the spacing between the lines of the "protein change" and "frequency" columns, so as one reads across a line it is difficult to determine which information corresponds with which polymorphism. For example, if one reads across the line which teaches the 1513 A→C polymorphism, it appears that the table is teaching that this is a "silent" polymorphism because the word "silent" appears to be directly next to the 1513 A→C line. However, if one counts down from the first polymorphism in exon 13 the 1513 polymorphism is the fifth listed, and if one counts to the fifth description in the "protein change" column, one finds that the fifth entry is "glu496ala." The misalignment of the columns makes the table very difficult to interpret.

Appropriate correction is required.

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, for example "Detection of polymorphisms in the human P2X₇ gene."

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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9. Claims 14-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14-21 are indefinite because the preamble of claim 14 recites a method for determining the presence or absence of a single nucleotide polymorphism, but the method steps of the claims do not clearly set forth that this recited goal is accomplished. For example, claim 14 recites a final process step requiring a step of testing the sample to determine the identity of the nucleotide. The claims do not clarify how the testing step which results in determining the identity of the nucleotide results in determining the presence or absence of a single nucleotide polymorphism. That is, it is unclear how one practicing the invention knows from the testing step whether one has in fact determined the presence or absence of a single nucleotide polymorphism.

Claim 14 is further indefinite because it is unclear what is meant by a position "corresponding" to position 1513 of SEQ ID NO: 2. Likewise, claims 22 and 25 recite this same language. Is applicant referring to position 1513 of SEQ ID NO: 2 or are other positions within SEQ ID NO: 2 within the scope of this recitation? To have a position "corresponding" to position 1513 of SEQ ID NO: 2, does a nucleic acid simply have to have 1513 nucleotides or is some other structural limitation implied by the use of this language? Claims which depend from claims 14 and 22 are indefinite over this recitation as well.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 14-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In claim 14, the recitation "in need of treatment with a therapeutic agent that is transported by P2X7" appears to be new matter. The specification does not provide basis for the concept of therapeutic agents that are transported by P2X7. The remarks filed with the amendment cite basis for claim 14 at pages 2 and 13. The cited recitation on page 2 (lines 21-30) do not mention therapeutic agents. Page 13 at lines 9-10 teaches that "a drug acting at P2X7 s that drug binding with P2X7 in humans is an important part of a drug exerting is pharmaceutical effect in man (lines 9-11)." This section does not teach therapeutic agents that are transported by P2X7. The recitation that a drug binds with P2X7 or "acts" at P2X7 (specification page 13, line 15) is not the equivalent of a drug that is "transported" by P2X7 because a drug could bind the receptor but not be transported, depending on where and how the drug binds the receptor. Since the specification does not discuss drugs that are "transported" by P2X7, the claims are rejected

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for having new matter. Claims 15-21 depend from claim 14, and these claims are also rejected for containing this new matter.

With regard to claims 18 and 19, the new limitation of “the nucleotide is not an A” in claim 18 and the recitation “the nucleotide is in a codon that does not encode a glutamate” in claim 19 appear to represent new matter. In applicant’s remarks filed with the amendment, applicant asserts that support for these claims can be found on page 8 in the second table. This provides basis for a limitation wherein the nucleotide at position 1513 of SEQ ID NO: 2 is an A or a C, however none of them provide specific basis for the limitation that the nucleotide is “not an A” or that the codon “does not encode a glutamate.” The table at page 8 recites “1513 A→C.” The language of these claims encompasses additional alleles at this position, and claim 21 additionally encompasses changes in the other nucleotides that are within the codon that position 1113 is a part of, providing that the changed “codon does not encode an glutamate.” Specifically, the exclusionary proviso in which the nucleotide is “not an A” or “does nor encode an glutamate” is not found in the specification. As noted by MPEP 2173.05(i),

“Any negative limitation or exclusionary proviso must have basis in the original disclosure. See *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983) *aff’d* mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.”

Since no explicit basis has been identified for the newly added negative limitation, claims 19 and 24 are rejected as incorporating new matter.

12. Claims 14-25, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

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described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention and Breadth of the Claims

The claims are all drawn to methods which include a step of detecting a single nucleotide polymorphism within the human P2X7 gene. The particular polymorphism is an A→C transition at position 1513 of SEQ ID NO: 2. Rejected claims 14-21 and 25 require that the nucleic acid sample assayed be obtained from a “human identified as in need of treatment with a therapeutic agent that is transported by P2X7.” Rejected claims 22-25 and 34 require that the nucleic acid sample be obtained from a person having or at risk of having a “P2X7 mediated disease.” Thus, the “use” of this invention requires the knowledge of the relationship between the polymorphism at position 1113 of SEQ ID NO: 4 and some phenotype, for example, a disease or response to a drug. Furthermore, the practice of the claimed invention requires the knowledge of “a therapeutic agent that is transported by P2X7,” or the knowledge of diseases which are in fact “P2X7 mediated.”

Rejected claims 14-21 require that the nucleic acid sample assayed be obtained from an individual identified as “in need of treatment with a therapeutic agent that is transported by P2X7.” Thus, the nature of the invention requires the knowledge of drugs that are transported by P2X7. Further, the implication of the claim is that the identity of the nucleotide will be useful for determining treatment for the human, and indeed, the specification states that “preferably determination of the status of the human is clinically useful (p. 13, line 7),” describing such utilities as determining what drug to administer or effective amounts of drugs. Most of the

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claims are sufficiently broad so as to encompass any possible drug that is “transported by P2X7,” and any reason for treatment with such a drug.

Rejected claims 22-25 and 34 require that the sample is from a human “having or at risk for developing an P2X7-mediated disorder.” Thus, the nature of the claimed invention requires knowledge of the identity of disorder which is in fact mediated by P2X7, but the claims are sufficiently broad to include any possible disorder that is so mediated. Dependent claim 23 narrows the scope of the disease to hyperlipoproteinemia or cardiovascular disease. Even this recitation is sufficiently broad so as to encompass many different diseases.

State of the Prior Art

The prior art teaches the nucleic acid sequence of the genomic and cDNA of the human P2X7 receptor, and that this receptor is a ligand-gated channel whose activation leads to an inward ionic current and cell permeabilization (see Buell *et al.* (1998) and Rassendren *et al.* (1997) and US 6133434, for example). Gu *et al.* further teach that this receptor is a ligand-gated channel that has been shown to mediate the ATP-induced apoptotic death of monocytes, macrophages, and lymphocytes (p. 3), and Gu *et al.* teach a single nucleotide polymorphism that is an A→C transition at position 1513. Gu *et al.* further teach that this polymorphism causes loss of function of the P2X7 polypeptide.

The prior art does not teach that any particular diseases are mediated by P2X7. In fact, Gu *et al.* identify the loss of function polypeptide to be present in 10 out of 45 normal, healthy subjects, demonstrating that even with loss of P2X7 patients remain healthy.

Baxter *et al.* (WO 99/29661) teach compositions that are effective as P2X7 antagonists, and teach that P2X7 “may” play a role in inflammatory, immune or cardiovascular diseases, but

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Baxter *et al.* do not teach that any of these diseases are mediated by P2X7. Their statement is a statement is essentially a prophetic statement that these types of diseases could be associated with P2X7, but they do not provide any evidence to support this assertion. Further, Baxter *et al.* are silent as to whether or not any of these drugs are transported by P2X7. The prior art does not teach any drugs that are transported by P2X7.

Direction Provided and Working Examples

The specification also teaches a single nucleotide polymorphism that is an A→C transition at position 1513 of SEQ ID NO: 2. The specification, at page 21 cites Gu *et al.* as teaching that this polymorphism causes loss of function of P2X7.

The specification further asserts that compounds acting on P2X7 are “indicated” as pharmaceuticals for a wide variety of conditions, including rheumatoid arthritis, diabetes, Alzheimer’s disease, stroke, varicose veins, and some cancers (p. 1). The specification does not provide any further guidance as to whether these diseases are in fact mediated by P2X7, or how to identify a risk of having such diseases. The specification does not provide any working examples of methods for identifying patients as having or at risk of having P2X7 mediated diseases. Furthermore, the specification does not disclose any relationship between P2X7 mediated diseases and the polymorphism at position 1513 of SEQ ID NO: 2. While the specification does refer generically to “P2X7 mediated” diseases, the specification does not particularly define what is required for a disease to be mediated by P2X7.

The specification does not teach that any of these compounds “acting” on P2X7 are in fact transported by P2X7. The specification does not teach any patients that are “identified as in need of treatment with a therapeutic agent that is transported by P2X7,” nor does the

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specification provide any criteria as to how to identify such patients or therapeutic agents that are transported by P2X7. The specification does not demonstrate the relationship between response to P2X7 and any drug; the specification fails to provide any data which suggests such a relationship exists.

The amount of direction or guidance presented in the specification with regard to how to use the instant invention is minimal. The specification asserts that the “knowledge of polymorphisms can be used to help identify patients most suited to therapy with particular pharmaceutical agents (p. 2),” but the specification does not provide any evidence that the polymorphism at position 1513 of SEQ ID NO: 2 is in fact correlated with patient response to any particular pharmaceutical agent. The specification asserts at page 3 that humans may be tested for predisposition or susceptibility for disease (lines 6-7), but the specification does not provide any evidence that the polymorphism is associated with any particular human disease. The specification asserts that the claimed methods can be used in the development of new drug therapies stating that “Identification of a link between a particular allelic variant and predisposition to disease development or response to drug therapy may have a significant impact on the design of new drugs (p. 7)” but again, the specification fails to provide of a link between a particular allelic variant and predisposition to disease development or response to drug therapy. That is, the specification does not provide any guidance as to how the polymorphism at position 1513 of SEQ ID NO: 2 would be associated with any pharmaceutical agent. The specification does not discuss whether this particular polymorphism will increase the likelihood of a positive or negative response to any drug. The specification provides no guidance or working examples that teach or demonstrate the ability to use the disclosed polymorphic site as a marker for any

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disease in particular, or for disease in general, or how to use the disclosed polymorphism to select a proper course of treatment of a disease.

Level of Skill and Level of Unpredictability

The level of skill in the art is quite high, but the unpredictability in the art is higher. There is no way of predicting which diseases, of the variety of possibilities proposed in the specification, are in fact “P2X7 mediated.” This is especially pointed out by the fact that Gu *et al.* observed that nearly a quarter of normal, healthy patients have at least one copy of the P2X7 gene which encodes a receptor with loss of function. Furthermore, in the post filing date art Dasgupta *et al.* were unable to identify an association between P2X7 polymorphisms and risk of chronic lymphocytic leukemia or with response to treatment, when trying to confirm previously demonstrated relationships. Li *et al.* were unable to detect a relationship between the 1513 polymorphism and tuberculosis, but were able to demonstrate an association between a promoter polymorphism and the protection against the disease. Thus, even within the P2X7 gene, Li *et al.* demonstrate that it is highly unpredictable as to whether or not a particular polymorphism will be associated with a phenotype, and even if one polymorphism in a gene is associated with the phenotype, a different polymorphism may not be. Thus, even when a relationship between the polymorphism and a disease state or response to treatment is noted in an isolated population, it is still unpredictable as to whether this indicates that the disease is mediated by the P2X7 gene or if it is merely a marker for the disease state.

There is also a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay

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identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β -globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The significance of the instantly disclosed P2X7 polymorphism remains highly unpredictable, as the instant specification demonstrates that healthy subjects carry this polymorphism. Thus determining how to use the claimed methods as asserted by applicant, requires the knowledge of unpredictable and potentially non-existent associations between the polymorphism and some disease or disease state. Even if the elected polymorphism is in some way associated with some disease, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the polymorphism is associated. That is, it is unpredictable as to whether the presence of a particular allele the polymorphism would confer a higher or lower likelihood of having the disease. In this case, the possible uses for the claimed

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methods are undefined, beyond the suggestion that they can be used to detect a disease associated with the P2X7 gene prior to treatment with a P2X7 drug. Furthermore, even when a relationship between the polymorphism and a disease state or response to treatment is noted in an isolated population, it is still unpredictable as to whether this indicates that the disease is mediated by the P2X7 gene or if it is merely a marker for the disease state.

Quantity of Experimentation

Absent any specific guidance from the specification or the prior art, in order to practice the claimed invention, one would have to undertake extensive studies to confirm the fact that the any particular disease, let alone all of the diseases encompassed by the recitation in claim 23, is in fact a "P2X7 mediated disease." One would have to undertake extensive biochemical analysis of patients who have the diseases in order to determine the etiology of the disease and the role of the P2X7 cation channel in the diseases.

In order to use the claimed invention as asserted by the specification, one would have to establish a relationship between the polymorphism at nucleotide 1113 of SEQ ID NO: 4 some disease state or some disease treatment method. Indeed, even to use the method of claim 14 to identify patients suited for particular pharmaceutical agents or to predict a disease, one would need to know that the polymorphism at nucleotide 1513 of SEQ ID NO: 2 was in some way associated with response to some pharmaceutical agent or some disease. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be

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unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method would be useful in disease detection and/or treatment, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the P2X7 1513 polymorphism and any disease or condition. Further, absent a teaching the polymorphism at position 1513 of SEQ ID NO: 2 is not associated with such conditions, it is further unpredictable as to whether detection of the polymorphism would be useful in predicting, e.g., the absence or decreased likelihood of such conditions.

Conclusion

Thus, in light of the nature of the invention, the scope of the claims, the lack of working examples, the lack of teaching in the prior art, the high level of unpredictability and the high level of experimentation necessary to determine which diseases are in fact "P2X7 mediated diseases" or which drugs are transported by P2X7 and how any of these drugs or diseases are related to the polymorphism at position 1513 of SEQ ID NO: 2, it is concluded that it would require undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

14. Claims 22 and 34 are rejected under 35 U.S.C. 102(a) as being anticipated by Gu *et al.* (JBC Papers in Press. Published on January 9, 2001 as Manuscript M010353200).

Gu *et al.* teach a method for determining the presence or absence of a single nucleotide polymorphism (SNP) in a P2X₇ gene, the method comprising:

(a) providing a nucleic acid from a human identified as having or at risk for having a P2X₇ mediated disease, wherein the sample comprises a nucleotide at a position corresponding to position 1513 of SEQ ID NO: 2; and

(b) testing to determine the identity of the nucleotide.

Specifically, Gu *et al.* teach methods in which DNA samples in the form of human leucocytes were obtained from 45 normal subjects and one patient with B-chronic lymphocytic leukemia (p. 6). The patient with B-chronic lymphocytic leukemia is considered to be a patient identified as having a P2X₇ mediated disease because, as recited in claim 16, such diseases include growth and metastases of malignant cells, which the patient with B-chronic lymphocytic leukemia has. However, Gu *et al.* do not specifically teach that this disease is a “P2X₇ mediated disease,” but it is considered to be within this group for the purposes of evaluating the prior art in light of Applicant’s disclosure. Gu *et al.* utilize DNA sequencing of PCR products (p. 6) to

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identify a single nucleotide polymorphism in the C-terminal tail of the P2X7 gene, specifically teaching the at the polymorphism is an A to C substitution at position 1513 (p. 9).

With regard to claim 34, the nucleic acid sample inherently a nucleotide at all of the positions required in the claim, as Gu et al. isolate total genomic DNA which would include the entire P2X7 gene. (p. 7).

Thus, the teachings of Gu *et al.* meet the limitations of all of the rejected claims.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al. in view of Newton *et al.* (Nucleic Acids Research (1989 April 11) 17(7)2503-2516).

Gu *et al.* teach a method for determining the presence or absence of a single nucleotide polymorphism (SNP) in a P2X₇ gene, the method comprising:

(a) providing a nucleic acid from a human identified as having or at risk for having a P2X7 mediated disease, wherein the sample comprises a nucleotide at a position corresponding to position 1513 of SEQ ID NO: 2; and

(b) testing to determine the identity of the nucleotide.

Specifically, Gu *et al.* teach methods in which DNA samples in the form of human leucocytes were obtained from 45 normal subjects and one patient with B-chronic lymphocytic leukemia (p. 6). The patient with B-chronic lymphocytic leukemia is considered to be a patient

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identified as having a P2X7 mediated disease because, as recited in claim 16, such diseases include growth and metastases of malignant cells, which the patient with B-chronic lymphocytic leukemia has. Gu *et al.* utilize DNA sequencing of PCR products (p. 6) to identify a single nucleotide polymorphism in the C-terminal tail of the P2X7 gene, specifically teaching the at the polymorphism is an A to C substitution at position 1513 (p. 9).

Gu *et al.* further teach determining the identity of the nucleotide at a position corresponding to position 1513 of SEQ ID NO: 2 via sequencing of PCR fragments (p. 7), but Gu *et al.* do not teach methods which use any of the techniques particularly recited in the rejected claims, for example ARMSTM.

However, at the time the invention was made there were a multiplicity of different methods for detection of single nucleotide polymorphisms, as are discussed in the specification at page 6. For example, Newton *et al.* teach a method for detecting single base changes that allows genotyping solely by inspection of reaction mixtures after electrophoresis. They call the method ARMSTM. (See abstract and throughout).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the polymorphism detection method taught by Gu *et al.* so as to have detected the polymorphism using the ARMSTM method taught by Newton *et al.* One would have been motivated to make such a substitution because Newton *et al.* teach many advantages of using the ARMSTM system, including that it is a simple and reliable and does not require a host of time consuming steps, such as sequence analysis of PCR products. Thus, in light of the teachings of Gu *et al.* in view of Newton *et al.* the claims are prima facie obvious.

Conclusion

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17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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Art Unit 1634

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